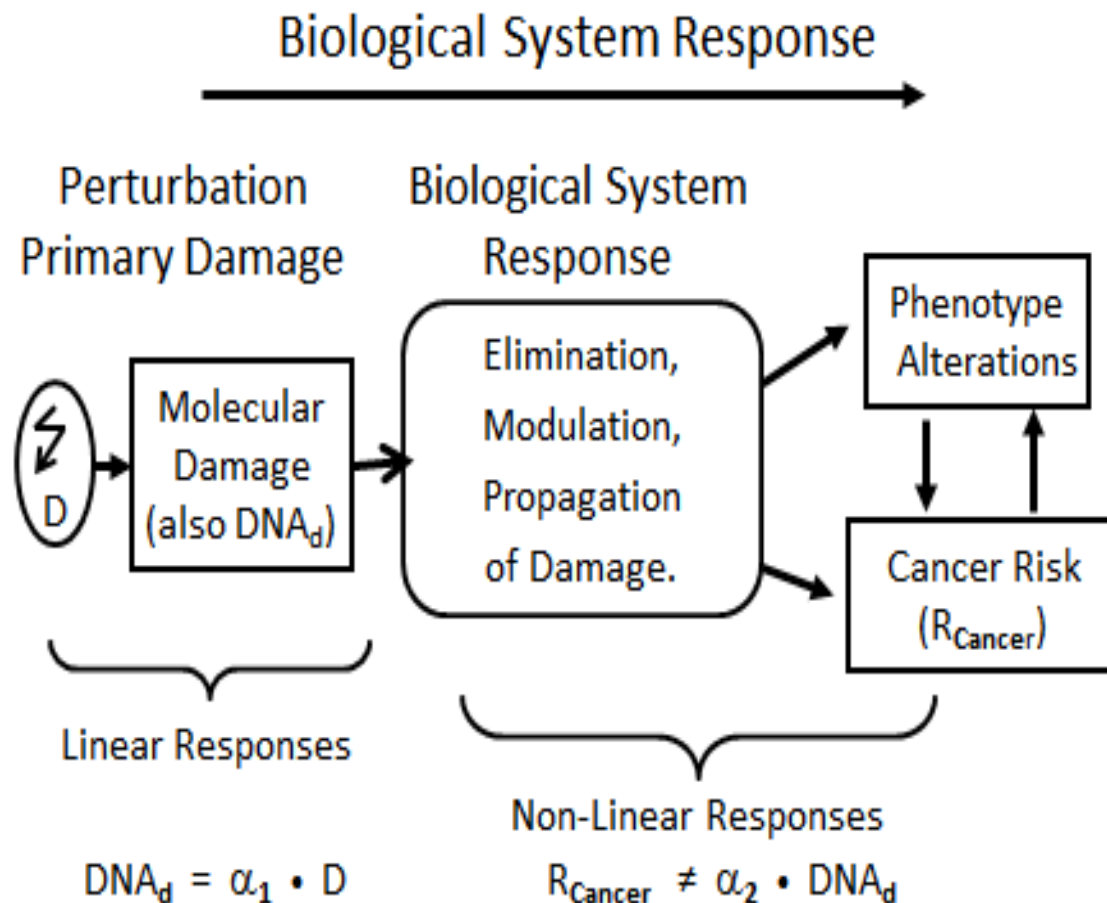


Biological Adaptive Protection

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Adaptive Protection

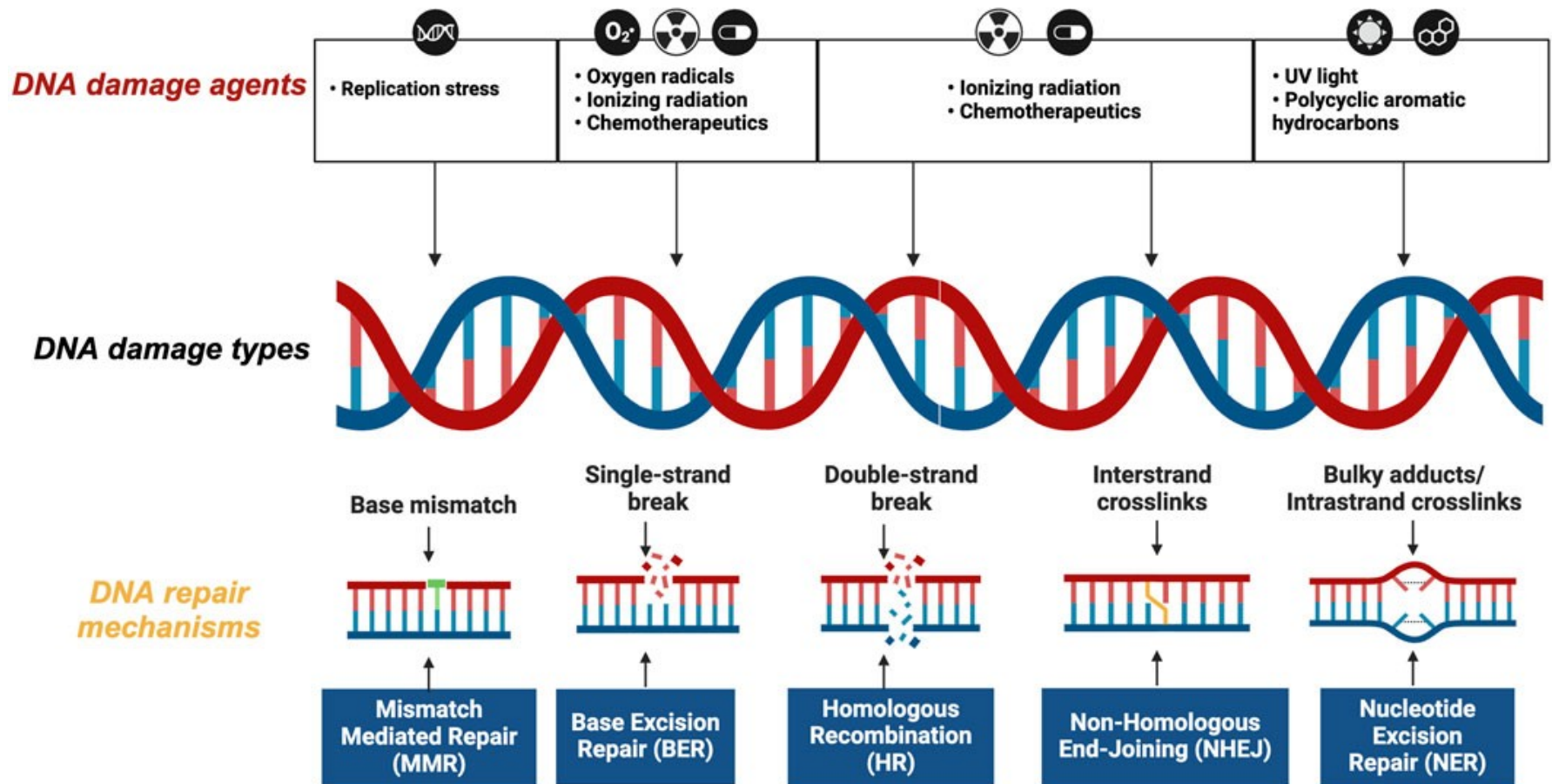


Adaptive protection is physiological expression of cellular capabilities to maintain tissue structure integrity and function when exposed to low levels of potentially harmful agents

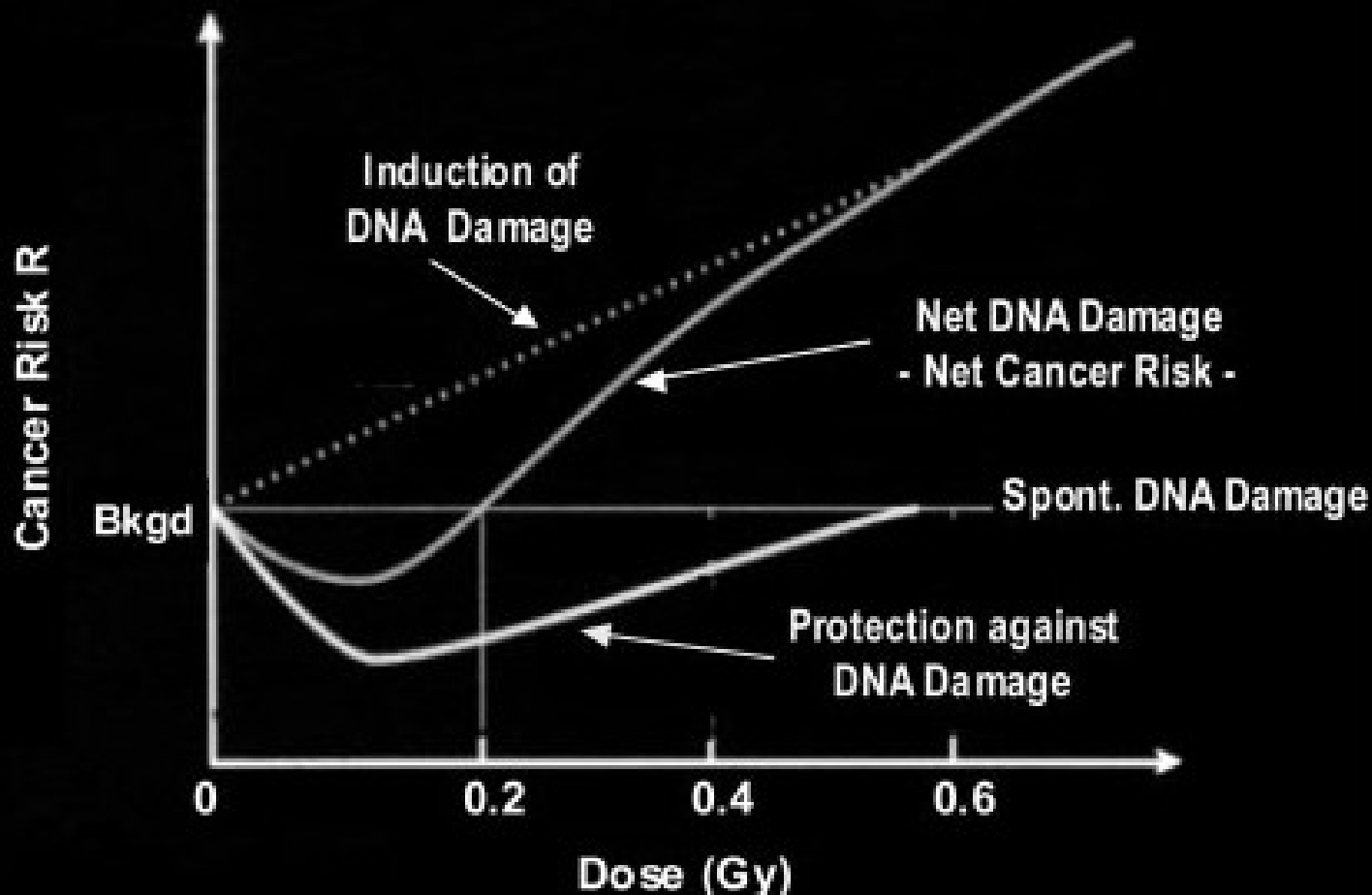
Adaptive Protection Responses

- ▶ DNA damage prevention – stimulation of free radical detoxification system to neutralize free radicals and reactive oxygen species (ROS)
 - Appears to reach maximum about 4 hours after exposure to stressor
 - Active for hours to weeks depending on tissue/cell type
- ▶ DNA damage repair – protection against chromosomal aberrations
- ▶ Apoptosis removal – programmed cell death
- ▶ Immune response stimulation

DNA Damage Repair Mechanisms



Dual Effect of Low Dose Ionizing Radiation



Ref. *Evidence for Beneficial Low Level Radiation Effects and Radiation Hormesis*, L.E. Feinendegen, MD, The British Journal of Radiology, 78 (2005), pp. 3-7

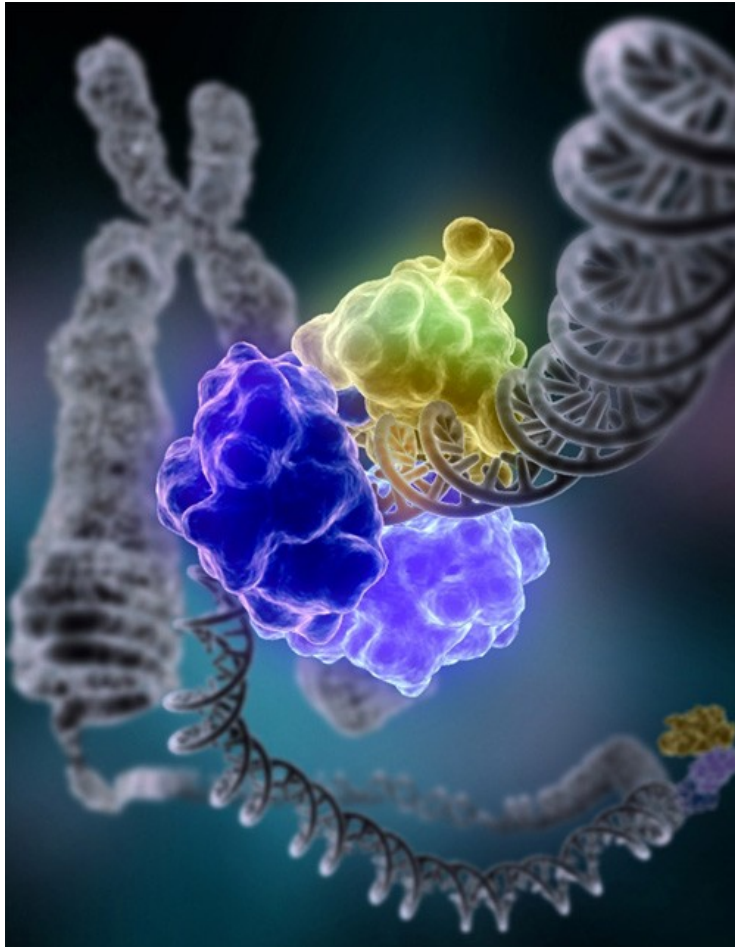
Adaptive Protection and Dose-Rate

- ▶ Response level of adaptive protection depends on radiation dose-rate, rather than accumulated dose
- ▶ Importance of dose-rate underscored by effectiveness of protracted radiotherapy treatment (i.e., fractionated doses)
 - Total radiation dose to cancerous tumor divided into several smaller (fractionated) doses over period of several days to allow body's adaptive protection system time to repair damage to surrounding normal cells between doses
- ▶ Although high chronic dose-rate (likely >1 mGy/hr) of ionizing radiation can inhibit body's adaptive protection system, low dose-rate, low-LET natural background radiation (≈ 0.0001 mGy/hr) does not
 - 1 mGy/hr effectively high chronic dose-rate threshold^a

Repair of DNA Damage

- ▶ Organisms cannot survive without full-time, intensive activity of powerful adaptive protection systems to prevent, repair, and remove metabolism-induced DNA damage
- ▶ Endogenous (i.e., spontaneous) rate of DNA damage from normal metabolism far exceeds rate of DNA damage caused by low-level ionizing radiation
- ▶ Cells have very efficient repair mechanisms to fix broken DNA (e.g., DNA repair enzymes)
- ▶ Damaged DNA migrates to special “repair centers” within cell, which put strands back together within hours

Repair of DNA Damage (cont.)



Special enzyme
encircling double helix
to repair broken strand
of DNA

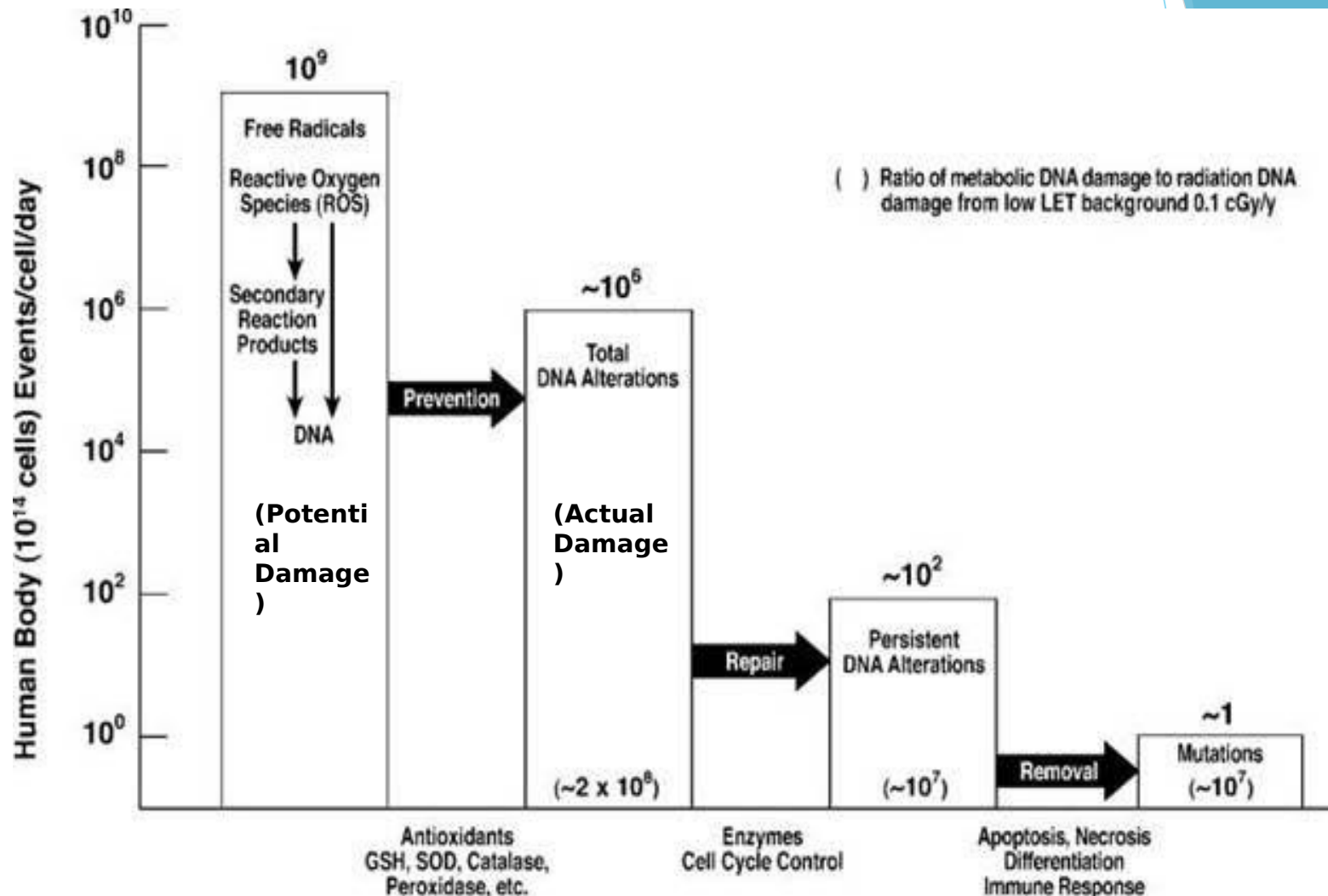
DNA repair begins in
seconds to minutes
after exposure

DNA repair times are
 ≈ 24 hours^a

Repair of DNA Damage (cont.)

- ▶ Double-helical structure of DNA ideally suited for repair because it carries two separate copies of all genetic information—one in each of two strands
- ▶ Each human cell contains multiple DNA repair systems, each with its own enzymes and preferences for type of damage recognized
- ▶ Most systems use the undamaged strand of double helix as template to repair damaged strand

DNA Damage Reduction by Cellular Prevention, Repair, and Removal Mechanism



Radiation Effects in Perspective

- ▶ DNA in human cells also damaged by normal biological functions (routine eating, breathing, stress of heat and exercise)
- ▶ Gene mutations (unrepaired or mis-repaired DNA damage) from normal metabolism outnumber those caused by natural low-dose radiation by 7 orders of magnitude (10^7)
- ▶ Even high acute radiation doses add only few more gene mutations to millions occurring from normal metabolism

Ref. James Muckerheide, paper presented at the 8th International Conference on Nuclear Engineering, held in Baltimore, April 2-6, 2000

Detoxification and Repair Processes Necessary for Life

Both biologically- and radiation-generated reactive oxygen species are completely intertwined in driving the inescapable need for all aerobic biological systems to have robust detoxification and repair processes in order to survive and thrive.

James Bus, PhD, DABT, Fellow ATS
Senior Managing Scientist in Exponent's Health
Sciences

Adaptive Protection Summary

- ▶ **All** organisms have powerful protection systems that react to stresses to heal injuries and destroy pathogens
- ▶ **All** organisms adapt to changing environmental stresses via changing adaptive protection system activity levels
- ▶ **All** organisms that breathe air (or consume oxygen for energy) suffer damage due to reactive oxygen species (ROS), and have protection systems that prevent damage, repair damage, and replace unrepaired cells/tissues
- ▶ **All** humans incur cell damage from non-radiation-induced causes orders of magnitude higher than that from low-level natural background radiation

Adaptive Protection Summary (cont.)

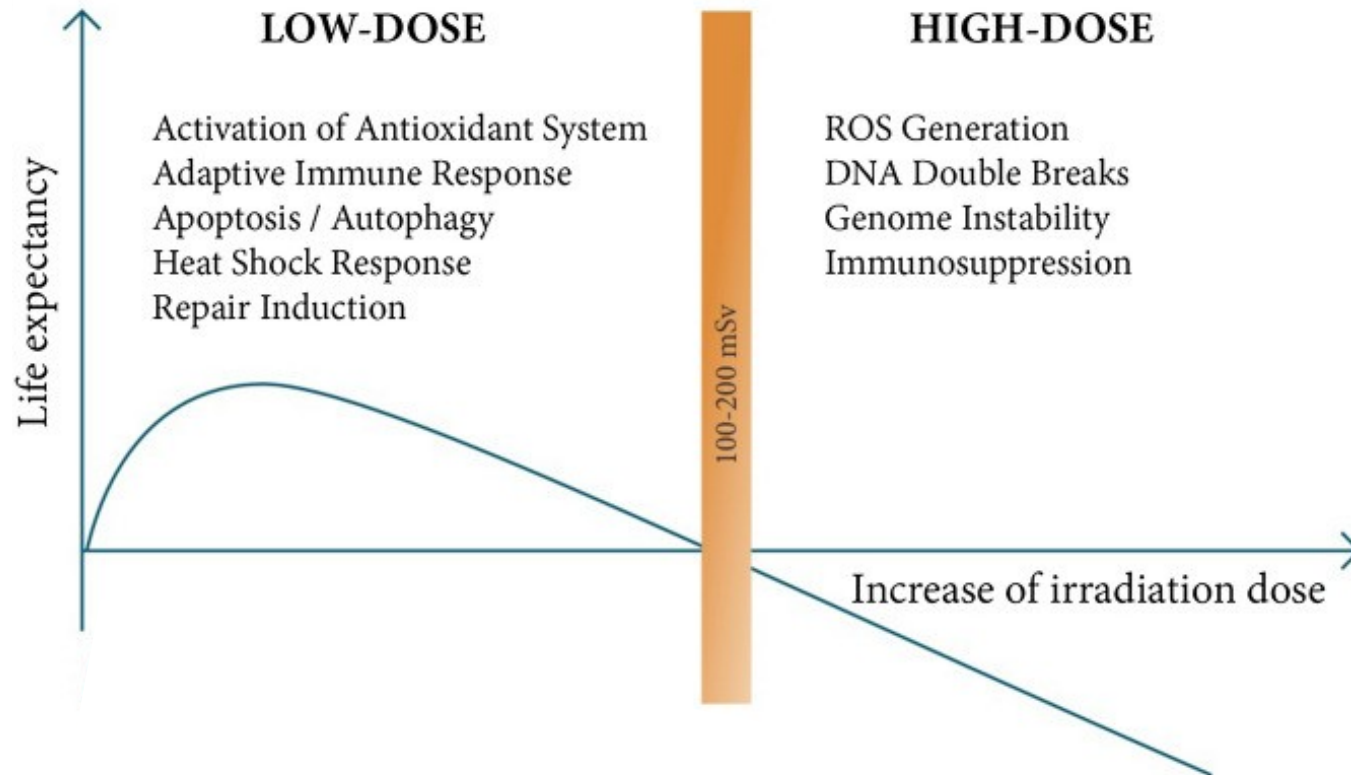
- ▶ For **all** humans, low radiation doses stimulate activity of adaptive protection system
 - Low-dose radiation providing optimum adaptive protection benefit varies from individual to individual
 - Increases in low-dose exposure beyond that associated with optimum adaptive protection benefit reduce effectiveness of protection until NOAEL achieved
 - Exposures beyond NOAEL become increasingly harmful due to radiation-induced inhibition or damage to adaptive protection mechanisms
- ▶ For **all** humans, radiation sensitivity affected by personal genetics, age, health, and other factors that cause optimum adaptive protection and NOAEL radiation doses to vary

Adaptive Protection In a Nutshell

No species that lacked the ability to repair damaged DNA could have emerged, much less reproduced, in a relatively high radioactive environment (compared to today) loaded with all sorts of other toxins as well.

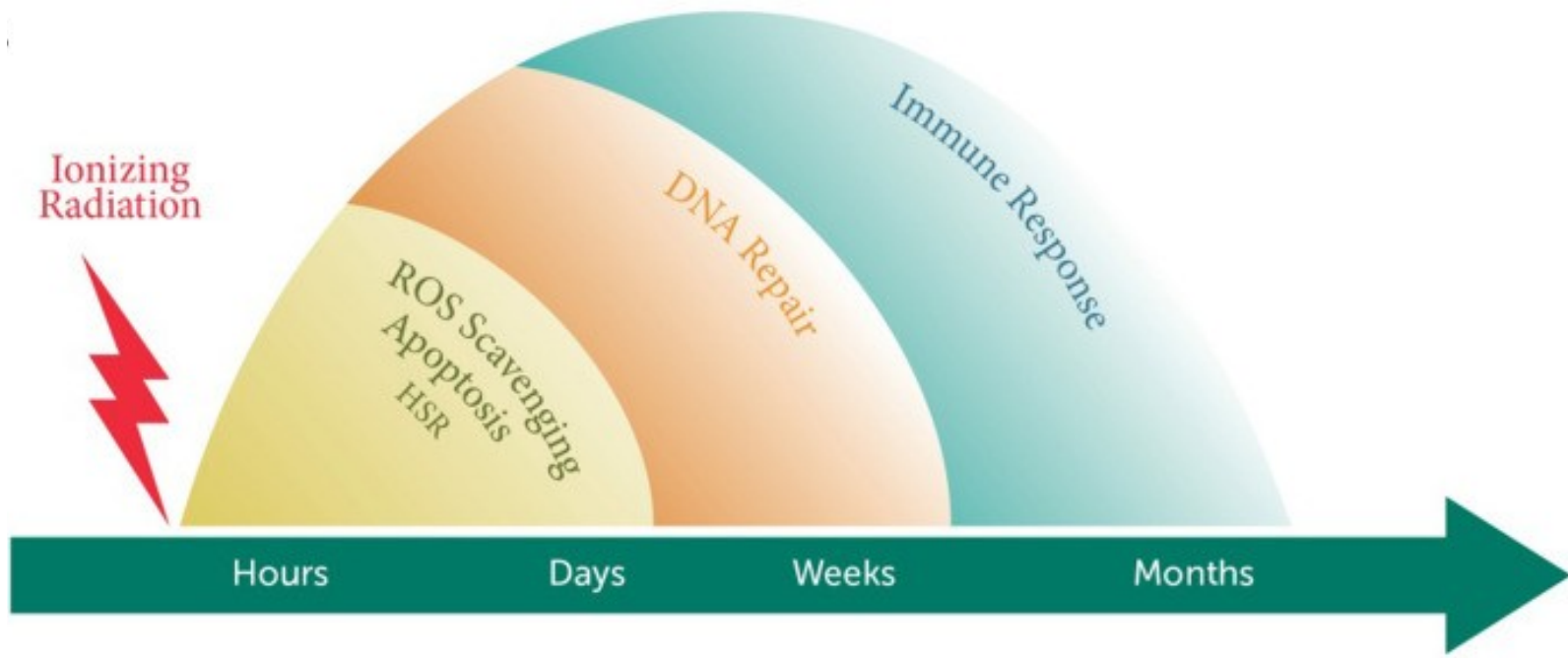
Supplemental Slides

Adaptive Protection Effectiveness



ROS - reactive oxygen species
mSv = mGy for low-LET
radiation

Adaptive Protection Timeline



ROS - reactive oxygen species
HSR - heat shock response

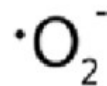
Reactive Oxygen Species (ROS)



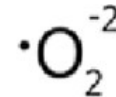
Oxygen



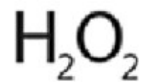
Superoxide anion



Peroxide



Hydrogen Peroxide



Hydroxyl radical



Hydroxyl ion



Free Radicals and ROS

- ▶ Highly reactive chemical molecules
 - Free radical is molecular species with unpaired electron
 - ROS is subset of free radicals containing oxygen atoms
- ▶ Byproducts of normal body metabolism; intrinsic to cellular functioning
- ▶ Also generated by external mechanisms
 - Ionizing radiation not even most prominent external mechanism
- ▶ Harmful free radicals neutralized by antioxidants